REMARKS

Status of the Claims

Claims 1-25 are pending in the application. Claims 13-15 and 20-15 have been withdrawn as drawn to a non-elected invention. Claims 16-19 have been canceled without prejudice. Claims 1-12 are currently under examination.

Claim Amendments

Claim 1 has been amended to clarify that the MELK polypeptide comprises SEQ ID NO: 6 and the MELK nucleic acid comprises sequence encoding SEQ ID NO: 6 and to clarify that the test agent modulates the activity or expression of MELK. Claim 1 has also been amended to include steps (d)-(f): (d) providing a second assay system comprising cultured cells expressing MELK capable of detecting a change in the RAC pathway; (e) contacting the second assay system with the test agent of step (b); and (f) measuring the RAC pathway in the presence or absence of the test agent, wherein the detection of a difference in the presence and absence of the test agent confirms the test agent as a RAC pathway modulating agent. Support for the amendment can be found throughout the specification and in original claim 16.

The claim amendments are made solely in an effort to advance prosecution and are made without prejudice, without intent to acquiesce in any rejection of record, and without intent to abandon any previously claimed subject matter. No new matter has been added by way of these amendments.

Withdrawal of Claim Objections

Applicants gratefully acknowledge the withdrawal of the claim objections to claims 1-19.

35 U.S.C. § 112, First Paragraph, Rejections

Enablement

Claims 1-12 and 16-19 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement because the claim(s) contains subject matter that was not described in the specification in such a way so as to enable one skilled in the art to which it pertains, or with which it is most closely connected, to make and/or use the invention. Claims 16-19 have been canceled, rendering the rejections moot as to those claims. With respect to claims 1-12, the Applicants respectfully traverse the rejections.

While the Office acknowledged the usefulness of the Applicants' genetic screen, it maintained the lack of enablement rejections because (1) in the absence of identified conserved region(s) of interaction between RAC and the 4B260 protein, one of ordinary skill in the art would not jump to the conclusion that any compound capable of modulating 4B260 is definitely involved in the RAC pathway (the Office believes more experiments are need to verify this conclusion); and (2) human MELK and the C. elegans 4B260 protein share 38% homology and therefore, according to the Office, one skilled in the art would not find it reasonable to screen and identify any (i.e., all) compound(s) having the ability to modulate a MELK peptide as a RAC pathway modulator (the Office believes that some compounds that modulate MELK will be falsely identified as potential modifiers of the RAC pathway).

Regarding the functional characterization of the 4B260 gene, Applicants reiterate the arguments submitted with the previous response (incorporated herewith), and, in particular, that the functional role of 4B260 as a modulator of the RAC pathway is clearly laid out in the specification. Ced-10 and mig-2 are two worm genes that are well established as worm counterparts of RAC pathway genes. Previous genetic studies have demonstrated that double mutant animals with defects in both the ced-10 and mig-2 genes show certain characteristic phenotypic defects which are indicative of loss of function of the RAC pathway in

the worm: (i) certain strong morphological and animal movement defects (uncoordinated movement, slow growth, vulval, withered tail and sterility defects), and (ii) short or misguided migration defects in specific mechanosensory neurons, the ALM and AVM cells. The RNAi based screen described in Example 1 of the specification demonstrates that RNAi of the 4B260 gene in either a ced-10 or mig-2 single mutant worms, but not wildtype worms, recapitulated both these same two phenotypes that are characteristic of defects in the worm RAC pathway, (i) the gross morphological and movement defects and (ii) the specific ALM and AVM neuron migration defects. Consequently this genetic analysis demonstrates **unambiguously** that worm gene 4B260 has a normal function that is similar to the normal function of the ced-10 and mig-2 genes; that is, the 4B260 gene normally functions to promote signaling in the worm RAC pathway. Furthermore, the RNAi results show that agents that block 4B260 function in the worm (in this case an inhibitory RNA homologous to 4B260) significantly reduce signaling in the worm RAC pathway. The worm RAC pathway genes ced-10 and mig-2 have human RAC pathway counterparts and therefore it can be extrapolated from the genetic results reported in the specification that inhibition of the human counterpart of worm 4B260 will similarly reduce RAC pathway function in human cells, including human cancer cells.

One skilled in the art of genetic screening would understand that the two screening assays used and described in the specification are evidence of a link between MELK and the RAC pathway. Specifically, Applicants have shown that inactivation of 4B260/MELK by RNAi results in Rac-associated (i.e., ced-10 or mig-2 associated) changes in neuronal cell migration. Therefore, agents that modulate MELK (inhibit or enhance MELK) can be used to identify candidate RAC pathway modulating agents.

In addition, the specification reports that human MELK was identified as the "ortholog" of worm 4B260 using blast analysis (the accepted criteria for orthology). Thus, MELK was identified as the human counterpart of the worm 4B260 gene, not because of an arbitrary percentage of sequence homology, but because the blast results demonstrated that of all human proteins human MELK

protein has the greatest percent homology to the worm 4B260 protein, and conversely, of all worm proteins, worm 4B260 protein has the greatest percent homology to human MELK protein. Moreover, in comparing human MELK and C. elegans 4B260 proteins, the 38% identity over the entire length of the protein is not only significant but extraordinary given the length over which the homologies are calculated and the great evolutionary distance between worms and humans (over 600 million years), and would lead a person skilled in the art to conclude that it can only reflect functional conservation. Applicants respectfully point out that no evidentiary basis has been provided by the Office for the assertion that 38% identity is not high enough to clarify functional conservation between a worm and human protein, which assertion Applicants submit is unfounded and contrary to scientifically-accepted teachings. For example, Doolittle, R.F., 1987, *OF URFS AND ORFS, A Primer on How to Analyze Derived Amino Acid Sequences*, University Science Books, Mill Valley, California, presents the homology criteria accepted in the art (chapter attached). The most relevant text is on page 12 where the author states under "Significance: Some Rules of Thumb":

> "At this point, let me offer some "rules of thumb" about degrees of confidence. If two sequences are longer than 100 residues, and are more than 25% identical after suitable gapping, it is very likely that the sequences are related". P. 12.

Finally, Applicants point out that the claims as amended require confirmation that the test agent is a RAC pathway modulator via the use of a second assay that measures changes in the RAC pathway in the presence and absence of the test agent. Applicants disagree with the Office's contention that it would impose undue experimentation to further verify that the identified compounds are associated with the RAC pathway. The specification provides numerous examples of assays, well within the skill of the ordinary artisan, that can be used for such verification. For example, the specification teaches (i) cell adhesion assays, (ii) cell migration/invasion assays, (iii) tubulogenesis assays,

and (iv) sprouting assays for verifying modulation of the RAC pathway at pages 26-29.

Applicants submit that the claimed methods are fully enabled for the reasons set forth above. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-12 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

Written Description

Claims 1-12 and 16-19 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement because the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 16-19 have been canceled, rendering the rejection moot as to those claims. The Applicants respectively traverse the rejections of claims 1-12.

The Office maintained the written description rejections, stating that Applicants had disclosed only one species, 4B260, of the MELK genus and therefore did not show possession of the entire genus. Without acceding to the merits of the rejection and solely to advance prosecution, Applicants have amended the claims to recite a single species of MELK polypeptide (SEQ ID NO: 6) and MELK nucleic acid (sequence encoding SEQ ID NO: 6) to be used in the screening assays, which structure (sequence) is fully known and described.

For the reasons indicated above, Applicants submit that the specification demonstrates possession of the claimed invention and thereby satisfies the written description requirement. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-12 under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement.

CONCLUSION

In view of the foregoing, the applicants respectfully request reconsideration of the pending claims. If it is believed that such contact would expedite prosecution of the present patent application, the Patent Office is urged to contact the undersigned.

Respectfully submitted,

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